

Interest of Prevention of Immediate Postpartum Hemorrhage with Misoprostol during Cesarean Section

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Abstract

Objective: The purpose of this study was to compare the efficacy of sublingual misoprostol to oxytocin for the prevention of Immediate Postpartum Hemorrhage (IPPH) during caesarian section in the Borgou Regional University Teaching Hospital (CHUDB).

Methods: It was a prospective randomized controlled clinical trial conducted over a period of 6 months from January 26 to July 26, 2015, on 230 female patients meeting inclusion criteria: cesarean section on term singleton pregnancy, under spinal anesthesia, without any bleeding. The patients were selected at random and divided into two groups: the first group had received 600 micrograms (μg) of misoprostol by sublingual route during umbilical cord clamping; the second one was administered 20 UI of oxytocin through intravenous route. The primary endpoint was drop in hematocrit. The secondary endpoints were drop in hemoglobin level, perioperative blood loss and postoperative complications.

Findings: The socio-demographic and obstetrical characteristics of both groups' patients were comparable. Average drop in hematocrit was identical: 0.05 ± 0.04 in both groups ($p=0.573$). The same applies to mean hemoglobin level: 1.7 ± 1.2 g/dl ($p=0.886$). As well, no significant difference was noted in average blood loss between the misoprostol group and the oxytocin group, respectively 281.8 ± 124.4 ml and 282.2 ± 120.8 ml ($p=0.271$). The incidence of side effects such as fevers and chills was significantly higher in the misoprostol group, respectively (79.1% vs. 9.6% and 79.1% vs. 0.0% $p<0.001$). However, those side effects were tolerable.

Conclusion: 600 μg of misoprostol dose by sublingual route is also as effective as oxytocin in the prevention of postpartum hemorrhage without significant side effects.

Keywords: Cesarean section; Sublingual misoprostol; Prevention; Postpartum hemorrhage

Introduction

Post-partum hemorrhage (PPH) is a leading cause of maternal mortality both in developed as well as in developed countries. Globally, the ratio of women giving birth to living infant with severe PPH is estimated at 11%. This incidence is considered to be significantly higher in developing countries [1].

For the prevention of immediate post-partum hemorrhage (IPHP), active management of labor is still regarded as being among the best practices and administration of uterotonics is by now the main component of it [2]. According to WHO, oxytocin is the uteronic drug of reference [2]. But oxytocin presents logistic constraints related to its conservation for it always requires being kept refrigerated [2]. Misoprostol is an uteronic drug which has a long shelf life and does not require refrigeration; it is therefore suitable for underprivileged context. It may be used without risk in women with hypertensive disorders [1]. In 2005 Vimala et al. [3] concluded that 400 μg sublingual misoprostol is also as effective as 20 IU of oxytocin infused. The sample size is relatively small. In 2012 the WHO recommended 600 μg misoprostol by oral route in the absence of oxytocin for IPPH

prevention after childbirth [2]. Sublingual route does not disturb cesarean section [4]. We undertook to perform a prospective randomized test in order to compare the efficacy of 600 μg misoprostol by sublingual route with oxytocin in IPPH prevention. The primary endpoint is reduction of perioperative blood losses objectively assessed based on drop in hematocrit.

Method

It was a prospective randomized clinical trial performed between January 26 to July 26, 2015 at the gynecology and obstetrics unit of the Borgou Regional University Teaching Hospital (CHUDB). This study involved female patients with ongoing singleton pregnancy, in which a cesarean section with loco-regional anesthesia was performed. The study excluded patients suffering of anemia with Hemoglobin level <8 g/dl, placenta previa, placental hematoma, Intra-uterine Fetal Death (IUFD), HELLP Syndrome, bleeding disorders, history of postpartum IPPH, history of uterine rupture, history of more than 2 cesarean sections.

Informed consent was taken from all subjects. Women were assigned randomly to receive either 600 μg misoprostol (3 tablets of misoprostol 200 μg) sublingually (group I) or 20 IU of oxytocin by intravenous (IV) route (10 IU used for IV injection and 10 IU diluted

into 500 ml of Ringer's lactate solution to be used in 30 minutes) (group II) after umbilical cord clamping. Randomization was done manually by the person responsible for the conduct of the study, generated random numbers and the randomized allocations were kept secure in opaque and sealed envelope. Just before the intervention, healthcare providers opened the envelope and thus registered the patient into one of the two groups.

An interviewer coordinated data collection on a questionnaire sheet. The primary endpoint in our study is drop in hematocrit (difference between preoperative hematocrit level and the one measured 48 hours after cesarean section). The secondary endpoints are : drop in hemoglobin (difference between preoperative hemoglobin level and the one measured 48 hours after cesarian section) ; blood loss estimated by direct method (sum of volume of blood sucked out in perioperative phase and amount of blood found in pads and surgical drapes); length of the procedure ; occurrence of adverse effects associated with administration of misoprostol or oxytocin and their degree of severity (low, moderate, severe) : temperature was measured using mercury thermometer 60 minutes (mn) and 90 mn after administration of the study treatment. Fever was defined by a temperature higher or equal to 38°C. Fever was said to be high when temperature was above 40°C. The mother characteristics were recorded on individual questionnaire. The data were collected by healthcare providers or brought by patients involved in the study after administration of uterotonic drug.

The study's sample size was calculated to detect difference in the reduction of hematocrit by 3% (difference considered to be clinically significant) in favor of misoprostol or oxytocin. For that value, required sample size was 250 patients, 125 patients in each group with a 90% statistical power and a p-value =5%. The demographic characteristics of both groups were studied as well as characteristics of pregnancy and cesarean section. The data were entered with EPIDATA software and processed using Epi-info software version 7.1.1.14. For this purpose, we chose p-value =0.05 as significance threshold.

Results

We selected 230 patients as participants to the study, distributed as follows: 115 in the oxytocin group and 115 in the misoprostol group.

Socio-demographic characteristics

There was no significant difference between the 2 groups as regards socio demographic characteristics. Cesarean section was the most common procedure performed: 50.4% in the misoprostol group versus 63.5% in the oxytocin group. But the difference was not significant (p=0.05); (Table 1). There was no difference between the 2 groups concerning the indications of cesarean section; (Table 2). As well, there was no significant difference in average length of time of cesarean section between misoprostol group and oxytocin group (32.6 ± 8.2 minutes vs. 33.30 ± 14.7 minutes; p=0.665) (Table 3).

Blood loss

Average blood losses estimated by direct method were similar in the misoprostol group compared to the oxytocin group without a statistically significant difference (281.8 ± 124.4 ml vs. 282.2 ± 120.8 ml, p=0.27160). No bleeding volume higher or equal to 1000 ml was found out in both groups of our study.

	Misoprostol (n=115)	Oxytocin (n=115)	p
Age (yr)	27.5 ± 5.1	27.5 ± 5.6	0.97
Parity	1.6 ± 1.5	1.6 ± 1.5	0.86
Gestational term (wk)	38.2 ± 1.8	38.1 ± 4.1	0.57
Pre-operative Hb level (g/dl)	11.8 ± 1.4	12.1 ± 1.3	0.16
Pre-operative Hct level	0.4 ± 0.04	0.4 ± 0.04	0.32
History of cesarean section			
Yes	52 (45.2)	46 (40.0)	0.42
No	63 (55.8)	69 (60.0)	
Type of cesarean section			
As emergency	58 (50.4)	76 (66.1)	0.01
Planned	57 (49.6)	39 (33.9)	
Type of anesthesia			
Loco-regional	115 (100.0)	115 (100.0)	1

Values in brackets indicate Data percentages
± means plus or minus (number or percentage)
Hb: Haemoglobin; Hct: Haematocrit; Yr: Year; Wk: Week

Table 1: Maternal demographics and procedure statistics.

Indications	Misoprostol (n=115)	Oxytocin (n=115)	p
History of cesarean section	19 (16.7)	22 (19.5)	0.61
Dystocia	43 (37.7)	40 (35.4)	0.68
HTA	13 (11.4)	12 (10.6)	0.83
Breech presentation	8 (7.0)	5 (4.4)	0.39
Fetal distress	23 (20.2)	27 (23.9)	0.52
Others	9 (7.8)	9 (7.8)	0.99

Table 2: Indications for cesarean section.

Paraclinical characteristics

There was no significant difference between mean pre-operative hemoglobin levels of misoprostol group and oxytocin group (11.8 ± 1.4 g/dl vs. 12.1 ± 1.3 g/dl, p=0.157). There was no significant difference between pre-operative hematocrit levels of misoprostol group and oxytocin group (0.4 ± 0.04 vs. 0.4 ± 0.04, p=0.320) (Table 1).

There was no significant difference between mean post-operative hematocrit levels of misoprostol group and oxytocin group (0.33 ± 0.05 vs. 0.3 ± 0.05, p=0.157). There was no significant difference between mean post-operative hemoglobin levels of misoprostol group and oxytocin group (10.1 ± 1.6 g/dl vs. 10.4 ± 1.6 g/dl, p=0.245) (Table 3).

Average decline in hematocrit level was similar for misoprostol group and oxytocin group without significant difference (0.05 ± 0.04

vs. 0.05 ± 0.04 , $p=0.573$). Average drop in hemoglobin level is not significantly different for misoprostol group and oxytocin group (1.7 ± 1.2 g/dl vs. 1.7 ± 1.2 g/dl, $p=0.886$) (Table 3).

	Misoprostol (n=115)	Oxytocin (n=115)	p
Blood loss (ml)	282.2 ± 122.4	282.2 ± 120.8	0.27
Average duration of cesarean section (mn)	32.6 ± 8.2	33.30 ± 14.7	0.66
Post-operative Hb level (g/dl)	10.1 ± 1.6	10.4 ± 1.6	0.245
Post-operative Hct level	0.3 ± 0.05	0.3 ± 0.05	0.157
Average drop in Hct level	0.05 ± 0.04	0.05 ± 0.04	0.573
Average Hb drop (g/dl)	1.7 ± 1.2	1.7 ± 1.2	0.886

Note: Hct: Hematocrit; Hb: Hemoglobin

Table 3: Factors associated with surgical procedure.

Side effects observed

Fever was mostly identified in the misoprostol group with a significant difference (79.1% vs. 9.6%, $p<0.01$) (Table 4). In most cases, it is a tolerable fever (75.7% in the misoprostol group vs. 9.6% in the oxytocin group). We identified 4 cases of high fever in the misoprostol group (3.5%). There was no case of high fever in the oxytocin group (Table 4).

Chills were mainly identified in the misoprostol group compared to oxytocin group, with a significant difference (79.1% vs. 0%, $p<0.01$). In more than half the cases there are tolerable (73.9%). Those chills were severe in 5.2% (Table 4). There was no significant difference in nausea and vomiting between the misoprostol group and the oxytocin group (Table 4).

Adverse effects	Misoprostol		Oxytocin		p
	n	%	N	%	
Fever	91	79.1	11	9.6	0.000
≥ 40°C	4	3.5	0	0.0	
Chills	91	79.1	0	0.0	0.000
Severe chills	6	5.2	0	0.0	
Nausea	3	2.6	0	0.0	0.2467
Vomiting	3	2.6	0	0.0	0.2467

Table 4: Synoptic table on the adverse effects observed in the two groups of the study.

Discussion

In our study, there was no significant difference in the perioperative hemorrhage estimated through three methods: drop in hematocrit, decline in hemoglobin level and blood loss volume estimated by direct method between the oxytocin group and the misoprostol group. Thus, misoprostol appears to be as effective as oxytocin in reducing bleeding.

The main objectives of this study have been achieved, as demonstrated by our results. Administration of 600 µg misoprostol by sublingual route during umbilical cord clamping is an alternative to oxytocin for IPPH prevention in case of cesarean section.

Unlike the other uterotonics which require a cold chain, misoprostol is stable at ambient temperature, low-cost and easy to use; makes it an ideal drug to use in certain circumstances. The WHO recommends it; when oxytocin is not available, it may be replaced by 600 µg misoprostol to be administered by oral route immediately after childbirth for prevention of IPPH [2]. Few studies assessed the use of misoprostol for IPPH prevention during cesarean section. Lapaire et al. found that 800 µg misoprostol administered by oral route is as effective as 20 IU oxytocin in reducing bleeding during cesarean section [5]. Lokugamage et al. also demonstrated in their study that 500 µg misoprostol administered by oral route appears to be an alternative to 10 IU oxytocin to reduce hemorrhage during cesarean section [6]. Only Zhao et al., comparing 600 µg misoprostol by oral route as the WHO recommends it to 40 IU oxytocin (20 IU into the uterine muscle and 20 IU by intravenous administration) found that misoprostol was more effective than oxytocin in hemorrhage reduction during cesarean section [7]. They worked on a relatively small sample. The difference between this study and ours is mainly on the route of administration of misoprostol. We administered the tablets of misoprostol by sublingual route. In several studies, misoprostol had been administered by different routes: oral, sublingual and rectal. Sublingual administration of misoprostol as once-daily therapy leads to a peak plasma levels 2 to 5 times higher than oral route, with a timeframe close to the one of oral route [8]. That route avoids the effect of first pass hepatic metabolism; it does not disturb the cesarean section procedure and ensures a continuous threshold of plasma concentration for a powerful action of uterotonics over a long period [4].

Blood loss

Blood losses were quantified by adding the blood volume in the suction jar and a visual estimation by the operator of amounts of blood in the pads used and surgical drapes or bed sheets. What was missing was weighing of pads as was the case in some studies [3,9]. We had no graduated bags for collecting blood lost in our hospital as

recommended in France [10]. Blood mixing with amniotic fluid may also make it difficult to measure the volume of blood lost. Blood losses are difficult to assess in case of cesarean section. Lapaire et al. demonstrated that visual estimation of blood loss undervalues the amount of hemorrhage by 30% compared to real losses [5]. To limit those factors we compared hematocrit and hemoglobin levels in pre-operative phase with the ones noted 48 hours after cesarean section. In this study, there is no difference in perioperative blood losses between misoprostol group and oxytocin group. Other authors also noted that there was no significant difference between the two groups concerning blood losses. Acharya et al. found out that estimated blood losses were 545 ml (IC 476-614) in the misoprostol group (400 µg by oral route) and 533 ml (IC 427-639) in the oxytocin group (10 IU by intravenous route) without significant difference ($p=0.85$) [11].

However, some authors recorded reduced blood losses with significant difference in the misoprostol group compared to the oxytocin group. For instance, Zhao et al. noted in China 212 ± 56.0 ml in the misoprostol group (600 µg by oral route) and 345 ± 64.7 ml in the oxytocin group (20 IU injected into the uterine muscle and 20 IU through intravenous administration) $p=0.01$ [7]. Vimala et al. found 819 ml in the misoprostol group (400 µg by sublingual route) versus 974 ml in the oxytocin group (20 IU injected by intravenous route) ($p=0.004$) [3]. Kumar et al. reported 595 ± 108 ml in the group of misoprostol (combined with Oxytocin) and 615 ± 118 ml in the group of placebo (combined with oxytocin) ($p=0.0015$) [4].

In our study, we did not find statistical significance in average drop of hemoglobin level in misoprostol and oxytocin group. Vimala et al. noted that declines in hemoglobin 24 hours after cesarean section were estimated at 0.4 ± 1.6 g/100ml in the group of misoprostol (combined with oxytocin) and 0.6 ± 1.8 g/100ml in the oxytocin group without a statistically significant difference ($p=0.56$) [3].

Kumar et al. reported that drop in perioperative hemoglobin level was significantly less important in the misoprostol group (400 µg sublingual) compared to placebo group in parturient women also receiving 20 IU of oxytocin by infusion (0.87 ± 0.29 g/dl versus 1.01 ± 0.26 g/dl $p=0.0016$) [4]. But the choice of hemoglobin as primary endpoint was criticized due to the variability of this parameter and particularly its early measurement within 24 hours after the surgical procedure [9]. The hematocrit that we assessed seems to be more adapted to this type of study [9,12].

In this study, there is no significant difference between the two groups concerning average drop in hematocrit. Comparing 400 µg misoprostol administered by sublingual route to 20 IU oxytocin by intravenous injection, Owonikoko et al. made the same remark in their series [13]. Fekih et al. noted that drops in hematocrit were lower in the group of misoprostol (combined with oxytocin) $1.10\% \pm 3.25$ than in the oxytocin group $4.30\% \pm 3.14$ with a statistically significant difference ($p<0.001$) [9]. Administered after childbirth, it seems that the combination of these two uterotonics helps reduce still further bleeding compared to each of the uterotonics used alone. This remark has been made by other authors in the literature [4]. Misoprostol and oxytocin may be administered together during labor period in order to prevent IPPH in case of risk factor for hemorrhages.

Characteristics related to cesarean section

All the cesarean sections were performed under spinal anesthesia in the two groups of the study. As the parturient woman was awake during that technique of anesthesia, this made possible the

administration of misoprostol tablets by sublingual route during umbilical cord clamping. It is the same type of anesthesia that had been used in previous studies [3,6,9,13]. In the study conducted by Kumar et al. cesarean section was carried out under spinal anesthesia in 94.4% of the cases in the misoprostol group and 92.8% in the one of oxytocin. In the other cases, epidural anesthesia was the type of anesthesia used [4].

There was no significant difference between the two groups as regards average duration of cesarean section. Most researchers made the same remark [2,9,14].

Side effects

Fever and chills are the most common adverse effects of misoprostol identified in 79.1% of the cases. These findings are higher than those published in the study of Vimala et al. [3] which pointed out a 26% rate; a 30% rate was found out in the study of Lokugamage et al. [6]. The high frequency of fever and chills pointed out in our study is related to the fact that we used higher doses of misoprostol and sublingual route of administration [8,15]. However, we recorded only 3.5% of high fever and 5.2% of severe chill. Wilfrido [16] who used the same dosage in his cohort for IPPH treatment reported 12.9% of high fevers and 2% of severe chills. Our lower rate of high fever may be associated with the fact that we systematically used paracetamol as analgesic drug in immediate post-operative phase. Actually, through its antipyretic action, paracetamol may reduce fever and chills associated with use of misoprostol.

This study is subject to potentially the following types of bias and limitations. We were limited by the study period. And the size of the obtained sample was 92% greater than 90% of the projected enrollment. Furthermore the participants were also divided into 2 groups. Therefore this lack of coverage does not invalidate the results. We do not record how much fluid Was Given During surgery; input and output during the study period. Hemodilution can be a major factor measuring haemoglobin and hematocrit.

Conclusion

600 µg misoprostol administered by sublingual route also appears to be as effective as 20 IU oxytocin in postpartum haemorrhage prevention. It may be an alternative to oxytocin in developing countries because of its advantages which are stability at ambient temperature, affordable cost, wide availability, long shelf life, security and effectiveness after sublingual administration. However, other studies are required to confirm our findings.

References

1. Abou-Zahr C (2003) The global burden of maternal death and disability. *Br Med Bull* 67: 1-11.
2. OMS (2014) Recommandations de l'OMS pour la prévention et le traitement de l'hémorragie du post-partum. Geneve: Organisation Mondiale de la Santé. Consulté le 10/01/2015.
3. Vimala N, Mittal S, Kumar S (2006) Sublingual misoprostol versus oxytocin infusion to reduce blood loss at cesarean section. *Int J Gynecol obstet* 92: 106-10.
4. Kumar S, Sanjay S (2012) Sublingual misoprostol to Reduce Blood Loss at Cesarean Delivery A Randomized controlled trial. *J Obstet Gynecol India* 62: 162-167.
5. Lapaire O, Schneider MC, Stotz M, Surbek DV, Holzgreve W, et al. (2006) Oral misoprostol versus intravenous oxytocin in reducing blood loss after emergency cesarean delivery. *Int J Gynaecol Obstet* 95: 2-7.

6. Lokugamage AU, Paine M, Bassaw-Balroop K, Sullivan KR, Refaey El, et al. (2001) Active management of the third stage at cesarean section: A randomized controlled trial of the third stage of misoprostol versus syntocinon. *Aust N Z J Obstet Gynaecol* 41: 411-414.
7. Zhao Y, Li X, Peng Y (1998) Clinical study on reduction of postpartum bleeding in cesarean section by misoprostol. *Zhonghua Fu Chan Ke Za Zhi* 33: 403-405.
8. Aubert J (2014) Pharmacologie du misoprostol (données pharmacocinétiques, tolérance et effet tératogènes). *J Gynecol Obstet Biol Reprod* 43(2) :114-22
9. Fekih M, Jenifene A, Fathallah K, Ben Regaya L, Memmi A, et al. (2009) Benefit of misoprostol of post-partum hemorrhage in cesarean section: A randomized controlled trial. *J Gynecol Obstet Biol Reprod* 38 : 588-93.
10. CNGOF, Collège National de Gynécologues Obstétriciens Français (2014) Recommandations pour la pratique clinique: Les hémorragies du post-partum (texte court). [En ligne].
11. Acharya G, Al-Sammarai MT, Patel N, Al-Habib A, Kiserud T (2001) A randomized controlled trial comparing effect of oral misoprostol and intravenous syntocinon on intra-operative blood loss during caesarean section. *Acta Obstet Gynecol Scand* 80: 245-250.
12. Hidar S, Jennane TM, Bouguizanne S, Lassoued L, Bibi M, et al. (2004) The effect of placental Removal method at cesarean delivery on perioperative hemorrhage : a randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol* 117: 179-182.
13. Owonikoko KM, Arowojolu AO, Okunlola MA (2011) Effect of sublingual misoprostol versus intravenous oxytocin on reducing blood loss at caesarean section in Nigeria: A randomized controlled trial. *J Obstet Gynaecol Res* 37: 715 -721.
14. Ugwu IA, Enabor OO, Adeyemi AB, Lawal OO, Oladokun A, et al. (2014) Sublingual misoprostol to decrease blood loss after cesarean delivery: A randomized controlled trial. *J Obstet Gynaecol* 34: 407-411.
15. Pacheco FHM, Zambrano Benítez CP (2013) Case report and literature review: Hyperpyrexia as side effect following the administration of sublingual misoprostol in the management of post-partum hemorrhage. *Rev colomb anesthesiol* 41: 65-66.
16. León W, Durocher J, Barrera G, Pinto E, Winikoff B (2012) Dose and side effects of sublingual misoprostol for treatment of postpartum hemorrhage: what difference do they make? *BMC Pregnancy Childbirth* 12: 65-71.